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Damage to the left uncinate fasciculus is associated with heightened schizotypal traits: A multimodal lesion-mapping study

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ABSTRACT

A growing body of evidence suggests that individuals with pronounced schizotypal traits also display particular neurophysiological and morphological features – notably with regard to left frontotemporal connectivity. However, the studies published to date have focused on subclinical subjects and psychiatric patients, rather than brain-damaged patients. Here, we used the French version of the Schizotypal Personality Questionnaire to assess schizotypal traits in a sample of 97 patients having undergone surgical resection of a diffuse low-grade glioma. Patients having received other neurooncological treatments (including chemotherapy and radiotherapy) were not included. A combination of ROI-based based voxel-wise and tract-wise lesion-symptom mapping and a disconnectome analysis were performed, in order to identify the putative neural network associated with schizotypy. The ROI-based lesion-symptom mapping revealed a significant relationship between the *cognitive-perceptual* (positive) dimension of schizotypy and the left inferior gyrus (including the pars opercularis and the pars orbitalis). Importantly, we found that disconnection of the left uncinate fasciculus (UF) was a powerful predictor of the positive dimension of schizotypy. Lastly, the disconnection analysis indicated that the positive dimension of schizotypy was significantly associated with the white matter fibres deep in the left orbital and inferior frontal gyri and the left superior temporal pole, which mainly correspond to the spatial topography of the left UF. Taken as a whole, our results suggest that dysconnectivity of the neural network supplied by the left UF is associated with heightened positive schizotypal traits. Our new findings may be of value in interpreting current research in the field of biological psychiatry.

1. Introduction

A growing body of evidence suggests that cortical and white matter abnormalities are involved in the pathophysiology of many mental disorders, and especially schizophrenia spectrum disorders (Andreasen et al., 1994; Ellison-Wright and Bullmore, 2009; Ellison-Wright et al., 2014; Hazlett et al., 2008; Lener et al., 2015; Shenton et al., 2010; van den Heuvel et al., 2010; Wright et al., 2000). Along with the grey matter alterations in frontal and temporal structures frequently observed in these psychopathological conditions, a loss of integrity of frontotemporal white matter connections has also repeatedly been highlighted (for a review, see Ellison-Wright and Bullmore, 2009) – suggesting that brain disconnection may constitute the neural basis of the clinical symptoms, as previously suggested (Friston and Frith, 1995). This type of white matter disruption (as evidenced by a reduction in fractional anisotropy, a marker of tract integrity) has been observed not only in the uncinate fasciculus (UF) and the arcuate fasciculus (both of which link frontal and temporal areas) but also in others tracts - especially the inferior longitudinal fasciculus, the cingulum bundle and the fornix (Abdul-Rahman et al., 2011; Burns et al., 2003; Kawashima et al., 2009; Kubicki et al., 2005; Kubicki et al., 2002; Kunimatsu et al., 2012; Lener et al., 2015; Voineskos et al., 2010; Wheeler and Voineskos, 2014).

The "schizotypal personality" refers to the expression of schizophrenia symptoms in a non-clinical population (Raine, 2006). It is characterized by attenuated psychotic-like symptoms, such as unusual perceptual experiences, ideas of references, and odd beliefs (Raine, 1991). Schizotypy encompasses a constellation of personality traits

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that (following a factorial analysis) broadly correspond to the positive, negative and disorganized dimensions characterizing schizophrenia (Fonseca Pedrero et al., 2008; Raine et al., 1994).

At present, the literature data tend to suggest that schizotypy and schizophrenia have similar aetiological factors, with a possible overlap on the genetic level (Ettinger et al., 2014; Fanous et al., 2007) and the cognitive/behavioural level (Cochrane et al., 2012; Noguchi et al., 2008). For example, individuals with pronounced schizotypal traits show mild neurocognitive disorders resembling those observed in schizophrenia (Ettinger et al., 2015) - especially with regard to working memory (Matheson and Langdon, 2008), executive function (Louise et al., 2015), and sustained attention (Bergida and Lenzenweger, 2006; Chen et al., 1997). Likewise, schizotypal individuals display the same difficulties in predicting the sensory consequences of their actions as schizophrenia patients do (Asai et al., 2008; Lemaitre et al., 2016; Teufel et al., 2010).

Recent findings suggest that the above-mentioned similarities may extend to the neurophysiological level (Ettinger et al., 2014; Nelson et al., 2013). Indeed, a number of studies have highlighted morphometric differences by comparing the brains of participants displaying low vs. pronounced schizotypal traits. More specifically, some studies have observed a decrease in grey matter volume in the medial prefrontal cortex, orbitofrontal cortex, dorsolateral prefrontal cortex, insula, and superior temporal gyrus (DeRosse et al., 2015; Ettinger et al., 2012; Wang et al., 2015), whereas others have found an increase in grey matter density in the posterior cingulate cortex, right posterior middle temporal gyrus, cerebellum, and precuneus (Modinos et al., 2010; Wang et al., 2015). With regard to white matter pathways, schizotypal individuals present with abnormal frontotemporal connectivity (Nelson et al., 2011; Volpe et al., 2008). For example, low fractional anisotropy in the inferior fronto-occipital fasciculus and elevated inter-hemispheric asymmetry of the UF (amongst other features) were recently observed in a subclinical population (DeRosse et al., 2015).

Brain-damaged patients provide researchers with valuable insights into the neural pathogenesis of abnormal/deviant experiences in clinical and subclinical populations; these findings may also be of interest for the interpretation of psychiatric studies. Lesion mapping of personality dimensions (as assessed by self-questionnaires) has been successfully performed in the past (Barbey et al., 2014; Herbet et al., 2015; Operskalski et al., 2015). In the present study, we sought to establish links between schizotypal dimensions and brain structures (especially white matter structures). To this end, we assessed schizotypy in a large, homogeneous of patients having undergone surgical resection of diffuse low-grade glioma (DLGG) – a rare neurological tumour that has been proven especially useful for inferring the role of white matter connectivity in cognition (Herbet et al., 2014; Herbet et al., 2015; Herbet et al., 2016b). To process the behavioural data, we used a combination of voxel-wise and tract-wise lesion-symptom analysis; this approach generated converging evidence for a role of the left UF in positive schizotypy.

2. Methods

2.1. Participants

A total of 97 patients (with a mean ± standard deviation age of 41 ± 10.34 years; range: 18–66) having undergone surgical resection for diffuse low-grade glioma took part in this study. All the patients were recruited by the Department of Neurosurgery at Montpellier University Hospital (Montpellier, France), and were operated on by the same neurosurgeon (H.D.). The patients' medical records were systematically and carefully screened to identify and exclude patients with other neurological diseases (i.e. traumatic brain injury, stroke, multiple sclerosis, etc.) or psychiatric diseases (i.e. schizophrenia). In the same way, patients having received other neuro-oncological treatments (i.e. chemotherapy or radiotherapy) that could have affected cognition or behaviour were not included. The behavioural data were collected in the chronic post-treatment phase, i.e. at least three months after surgery (range: 3–72 months). All patients gave their written, informed consent to both participation in the study and the retrospective extraction of clinical and neuroanatomical data from their medical records. The study was conducted in compliance with the tenets of the Declaration of Helsinki.

2.2. The surgical procedure

In accordance with our standard procedures, all patients were operated on under the "awake" condition while direct electrostimulation was used to perform intraoperative functional mapping. This surgical technique has been extensively described previously (Duffau, 2005; Tate et al., 2014). It allows the surgeon to identify and thus spare the critical functional structures in the brain during the resection procedure – thus improving both the extent of the surgical resection and patients' quality of life by decreasing the risk of permanent neurological damage.

Briefly, once the cortex was exposed by craniotomy and dural opening, the tumour's boundaries were defined using intraoperative ultrasonography. Sterile letter tags were placed on the cortical surface for visual guidance during the surgical procedure. First, sensorimotor mapping was achieved while patients were performed a counting task in conjunction with a regular movement of the upper limb. This mapping was conducted with a bipolar electrode (tip-to-tip distance: 5 mm) delivering biphasic current (pulse frequency: 60 Hz; single pulse phase duration: 1 ms; amplitude: from 1 to 4 mA). A low-amplitude current (1 mA) was applied initially and then incrementally increased by 0.5 mA until a reproducible joint, motor or sensory impairment was evoked. This optimal threshold was used throughout the mapping session. Depending on the DLGG site, several functions were monitored intraoperatively via a variety of behavioural tasks, including language, motor, spatial and visual cognition, reading and emotion recognition tasks. Cortical mapping was followed by subcortical mapping throughout the surgical procedure.

2.3. Assessment of schizotypy traits

The French version of the Schizotypal Personality Questionnaire (SPQ) (Dumas et al., 2000; Raine, 1991) was used to assess schizotypy traits. This validated self-questionnaire is composed of 74 choice-forced items (Yes/No) grouped in three dimensions (cognitive-perceptual, interpersonal and disorganized subscales), which broadly correspond to the positive, negative and disorganized dimensions that characterize schizophrenia (Raine et al., 1994). Each dimension is formed from different subscales (9 in total), which correspond to the different criteria for schizotypal personality given in the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1987, DSM-III R). This self-questionnaire has excellent internal consistency - especially in its French version (Dumas et al., 2000).

2.4. Neuroanatomical data acquisition

Structural MRI datasets were acquired when the patient underwent a standard behavioural assessment in our university hospital. For the purposes of the present study, high-resolution three-dimensional T1-weighted images were extracted from this large set of neuroanatomical data. The images were acquired using either a 1.5 T Siemens Avento scanner (for 84.5% of the patients) or a 3 T Siemens Skyria scanner (for 15.5% of the patients) (both from Siemens Medical Systems).

2.5. Lesion drawing and normalization

Individual anatomical MRI scans were made to conform to standard stereotaxic space (Montreal Neurological Institute (MNI) space) using cost-function masking (Brett et al., 2001); this method is known to be the best normalization option for large lesions (Andersen et al., 2010).

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